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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/671,747	09/24/2003	Peter Martin Fischer	CCI-027CN	9353

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LAHIVE & COCKFIELD, LLP.
28 STATE STREET
BOSTON, MA 02109

EXAMINER

RAO, DEEPAK R

ART UNIT PAPER NUMBER

1624

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/671,747	FISCHER ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 January 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 and 35-48 are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 24-28 and 39 are allowed.
- 6) ☒ Claim(s) 1-5, 9-11, 29, 35-38 and 40-48 are rejected.
- 7) ☒ Claim(s) 6-8 and 12-23 are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This office action is in response to the amendment filed on January 3, 2005.

Claims 1-29 and 35-48 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

1. Claims 35-38, 42-45 and 46-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating lung cancer, does not reasonably provide enablement for treatment of all types of diseases of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant first argues that 'the instant claims are fully enabled as they are directed to methods of treating CDK dependent proliferative diseases by administering a compound of formula I'. However, it is once again submitted that existence of a single therapeutic agent for treating proliferative diseases associated with all types of CDK is contrary to the present understanding of oncology. A detailed analysis of the *Wands* factors was provided in the

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previous office action, which continues to be applicable to the pending claims.

Applicant argues that 'applicant teaches methods for determining the ability of the compounds to inhibit a panel of protein kinases (e.g., Example 17)', however, the instant claim recites '.... to inhibit at least one CDK enzyme' and therefore, encompasses all members of the CDK family. Applicant provides sources for the enzymes CDK2/cyclin E, but are silent as to the sources of others intended by the instant claims. The test example and results are also provided only for CDK2/cyclin E. There is neither data on how many compounds were tested nor data on which other CDK enzymes were inhibited and which ones were not. Applicant did not state on record or provide any guidance that the assays provided are correlated to the clinical efficacy of the treatment of various disorders encompassed by the claims. As can be seen from specification pages 21-22, the *in vitro* data holds significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired inhibition of the CDK enzymes. Further, the state of the art (see Blain) is indicative that 'the specific functions of Cdk are poorly understood'. Further, Lu Valle reference provides that "To obtain a more detailed understanding of chondrocyte proliferation and differentiation, much more work in this field will be necessary. The pathways connecting the mentioned growth factors to cell cycle genes, as well as negative regulation of these genes, have to be analyzed in much more detail" (see page 12).

Applicant's argument that 'the specification describes an assay (Example 18) to show the antiproliferative effects of the compounds' is fully considered. The human tumor cell lines used in the test assays are of lung cancer cell line and there is no disclosure regarding how this data is extrapolated to the treatment of all types of proliferative diseases associated with CDK. LuValle

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reference provides that “due to the complex biology of the skeleton *in vivo*, the results obtained in such studies will have to be confirmed by experiments using transgenic or “knockout” mice to contribute more significantly to our understanding of growth plate function”. This clearly illustrates the unpredictability of cell cyclin dependent kinase pathways and mechanisms and therefore, one skilled in the art would not reach the conclusion whether or not the compound will be effective in treating cancer, without going through undue experimentation.

While the specification provides sufficient enabling disclosure for the synthesis of the instantly claimed compounds, does not provide an enabling disclosure sufficient to cover the entire scope of the methods of use recited in the instant claims. The instant claims include ‘treating a CDK dependent proliferative disease by administering a compound sufficient to inhibit at least one CDK enzyme’ and therefore, covers ‘treatment of several types of diseases having diverse mechanisms - affecting different organs and having different methods of growth or harm to the body, and different vulnerabilities’. For example, the development of the most efficacious strategy for the treatment of cancers is based on understanding the underlying mechanisms of carcinogenesis. This includes the knowledge that the carcinogenic process is a multi-step, multi-mechanism process and that no two cancers are alike, in spite of some apparent universal characteristics, such as their inability to have growth control, to terminally differentiate, to apoptose abnormally and to have an apparent extended or immortalized life span. Since tumor promotion phase involves multiple mechanisms, there is no existence of a single therapeutic approach.

Contrary to applicant's argument that ‘the skilled artisan would be able to appreciate which CDK dependent proliferative diseases would be treated with the antiproliferative effect of

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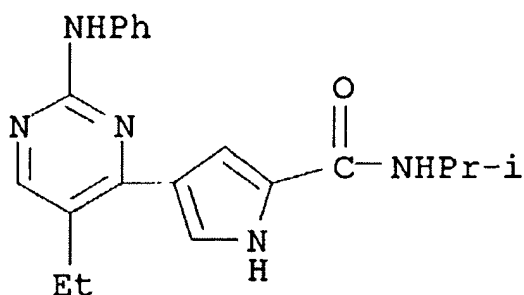
the claimed compounds', the examples in the disclosure are pertinent to tests that show that the compounds are effective in inhibition of CDK2/cyclin E. The specification does not provide any disclosure wherein the compounds are tested for CDK generally or the efficacy in treating any of the related diseases or disease symptoms associated with CDK. Applicant has not provided sufficient evidence that establishes that the disclosure would have enabled for one skilled in the art at the time of filing. Further, the state of the art does not identify a single class of compounds that can treat all types of diseases of the instant claims. Further, one skilled in the art of medicinal therapy recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to the carcinogenic process, making it even more challenging to have a single therapeutic agent for the treatment of diverse diseases. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule. A detailed understanding of the molecular mode of action of the kinase inhibitors alongside the elucidation of the molecular pathology of individual cancers is required to identify tumor types and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to receptor response endpoints. Therefore, it is maintained that applicants have not provided sufficient test assays or data to support the method of inhibition or treatment commensurate in scope with the claims, as of the filing date of the application.

For all the above reasons, the rejection is maintained as applied to the new claims 42-48.

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2. Claims 1-2, 29 and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al., U.S. Patent Application Publication No. 2003/0092714 (effective filing date February 9, 2001). The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'the reference does not provide biological data for compound 119 and therefore teaches away from the instant invention'. However, the reference clearly teaches a compound that differs only by the position of a substituent on the pyrimidinyl group – structural formula of compound 119 disclosed in the reference is depicted below for convenience:



The above compound of the reference differs from the instantly claimed genus by the position of the ethyl group which is at the 5-position as compared to the R³ of the instant formula I is at the 4-position. The reference teaches that the compounds are useful as pharmaceutical therapeutic agents having protein kinase inhibitory activity. It is to be noted that rejection under 35 U.S.C. 103 is proper where the subject matter claimed "is not *identically* disclosed or described" in the prior art, and the prior art directs those skilled in the art to the compounds, without any need for picking, choosing, and combining various disclosures. See *In re Shaumann et al.*, 572 F.2d 312, 315, 316, 197 USPQ 5, 8, (CCPA 1978). Further, the reference

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teaches that the compounds are useful as pharmaceutical agents, which is sufficient to one of ordinary skill to make the claimed compounds because similar properties are normally presumed when compounds are very close in structure. Where the specific compound falls within the ambit of a “very limited number of compounds”, the fact that a specific embodiment is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.” *In re Lamberti*, 545 F.2d 747,750, 192 USPQ 278, 280 (CCPA 1976). “The question under 35 U.S.C. 103 is not merely what the reference expressly teaches but what it would have suggested to one of ordinary skill in the art at the time the invention was made.”

“Structural relationships provide the requisite motivation or suggestion to modify known compounds to obtain new compounds.” See *In re Duel*, 51 F.3d at 1558, 34 USPQ2d at 1214. The closer the physical and chemical similarities between the claimed species or subgenus and any exemplary species or subgenus disclosed in the prior art, the greater the expectation that the claimed subject matter will function in an equivalent manner to the genus. See *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904. “An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.” *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). Reference must be considered, under 35 U.S.C. 103, not only for what it expressly teaches but also for what it fairly suggests; all disclosures of prior art, including unpreferred embodiments, must be considered in determining obviousness. *In re Burckel*, 201 USPQ 67 (CCPA 1979).

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The following rejections are necessitated by the amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "R⁴-R⁸ is selected from carbamoyl,.... " in lines 10-11. There is insufficient antecedent basis for this limitation in claim 1 on which claim 2 is dependent. The above term is not included in the definition of R⁶ in claim 1.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Torley et al., EP 233461. The reference teaches pyrimidinyl compounds, see formula in page 2, and the corresponding compounds in Tables. The reference compounds are taught to be useful – pharmaceutical therapeutic agents, see the abstract. The instant claims exclude some of the reference disclosed compounds, see the proviso statement, however, include compounds that differ by a –CH₂ group, i.e., wherein any of the groups are substituted by a methyl. For example, the instant claims exclude the reference disclosed compound of N-phenyl-4-(1H-pyrrol-2-yl)-2-pyrimidinamine, however, include compounds wherein the phenyl is substituted with, say, a 2-

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methyl group or the pyrrole is substituted with a methyl group, etc. Therefore, the instantly claimed compounds differ from the reference compounds by a -CH₂ group and it is well established that compounds that differ by a -CH₂ group are structural homologs. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homolog. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results. *In re Hass*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

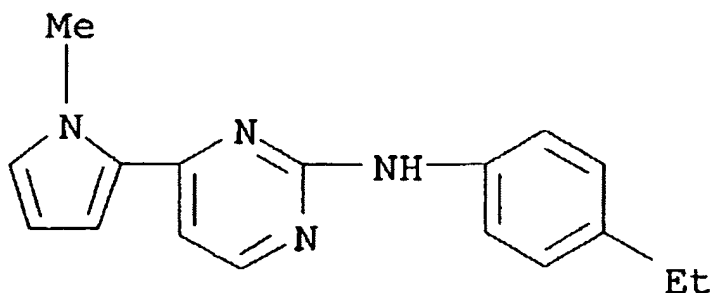
Applicant's arguments in reference to the 103 rejection over Torley in the response have been fully considered but they were not deemed to be persuasive. Applicant argues that 'the reference neither teaches nor suggests the use of the compounds for the treatment of CDK dependent proliferative disorders'. However, the prior art need not disclose the newly discovered property in order for there to be a *prima facie* case of obviousness. In fact, similar properties may normally be presumed when compounds are very close in structure. Also note, there is no requirement that the prior art must suggest that the claimed compound will have the same or similar utility as that discovered by applicant in order to support a legal conclusion of obviousness. *In re Dillon*, 919 F.2d 688, 696, 16 U.S.P.Q.2d 1897, 1904 (Fed. Cir. 1991). If the prior art compound does in fact possess a particular benefit, even though the benefit is not recognized in the prior art, applicant's recognition of the benefit is not in itself sufficient to distinguish the claimed compounds from the prior art. The reference teaches a use for the

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compounds, which is sufficient to one of ordinary skill to make the claimed compounds because similar properties are normally presumed when compounds are very close in structure. There is nothing on the record to show that the reference compounds do not possess the activity of the instant compounds. Applicants must prove that their compounds possess a property that the prior art compounds do not possess. The discovery of additional use not disclosed in the reference does not make otherwise obvious compounds unobvious. See *In re Best*, 195 USPQ 430 (CCPA 1977). The PTO can require an applicant to prove that the relevant prior art products do not necessarily or inherently possess characteristics of the claimed product. As there is no comparative data on record clearly establishing that the properties of the instant compounds are “unexpected” when compared to those of the reference compounds, the rejection is maintained.

The following rejections are under new grounds:

Claims 1-5, 9-11 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Torley et al., EP 233461. The reference teaches compounds of pyrimidyl compounds, see the formula in page 2 wherein the R₃ is a 1H-pyrrol-2-yl and further, the compounds in the Tables having the group (an exemplary compound of the reference depicted below for convenience):



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The reference compounds have 2-position of the pyrrolyl group attached to the pyrimidine. The instantly claimed compounds on the other hand, have the pyrrolyl attached to the 3-position of the ring. The reference compounds are taught to be useful as pharmaceutical agents, see the abstract. Since the instantly claimed compounds differ only by the position of the substituent group, they are positional isomers of the reference compounds. It would have been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are isomers of the reference compounds. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally isomeric compounds are suggestive of one another and would be expected to share similar properties and therefore, the same use as taught for the reference compounds. It has been held that a compound which is isomeric with a compound of prior art is prima facie obvious absent unexpected results. *In re Finley*, 81 USPQ 383 (CCPA 1949); *In re Norris*, 84 USPQ 458 (CCPA 1950). *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990).

Allowable Subject Matter

Claims 24-27, 39 and 28 are allowed. Claims 6-8 and 12-23 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

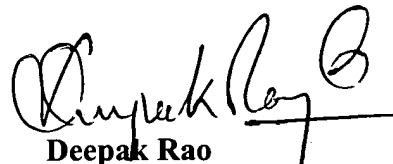
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Deepak Rao
Primary Examiner
Art Unit 1624

March 22, 2005